

# Preclinical efficacy and clinical translatability of Elafibranor in the GAN diet-induced obese and biopsy-confirmed mouse model of NASH



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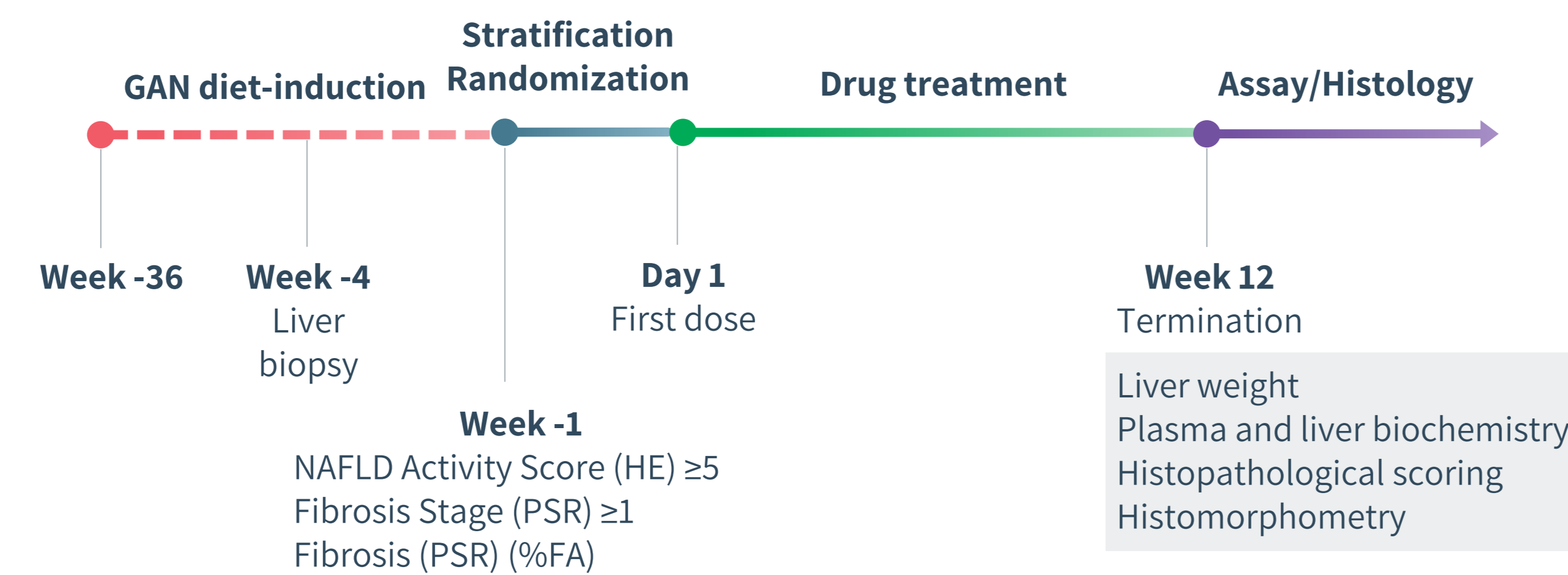
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## BACKGROUND & AIM

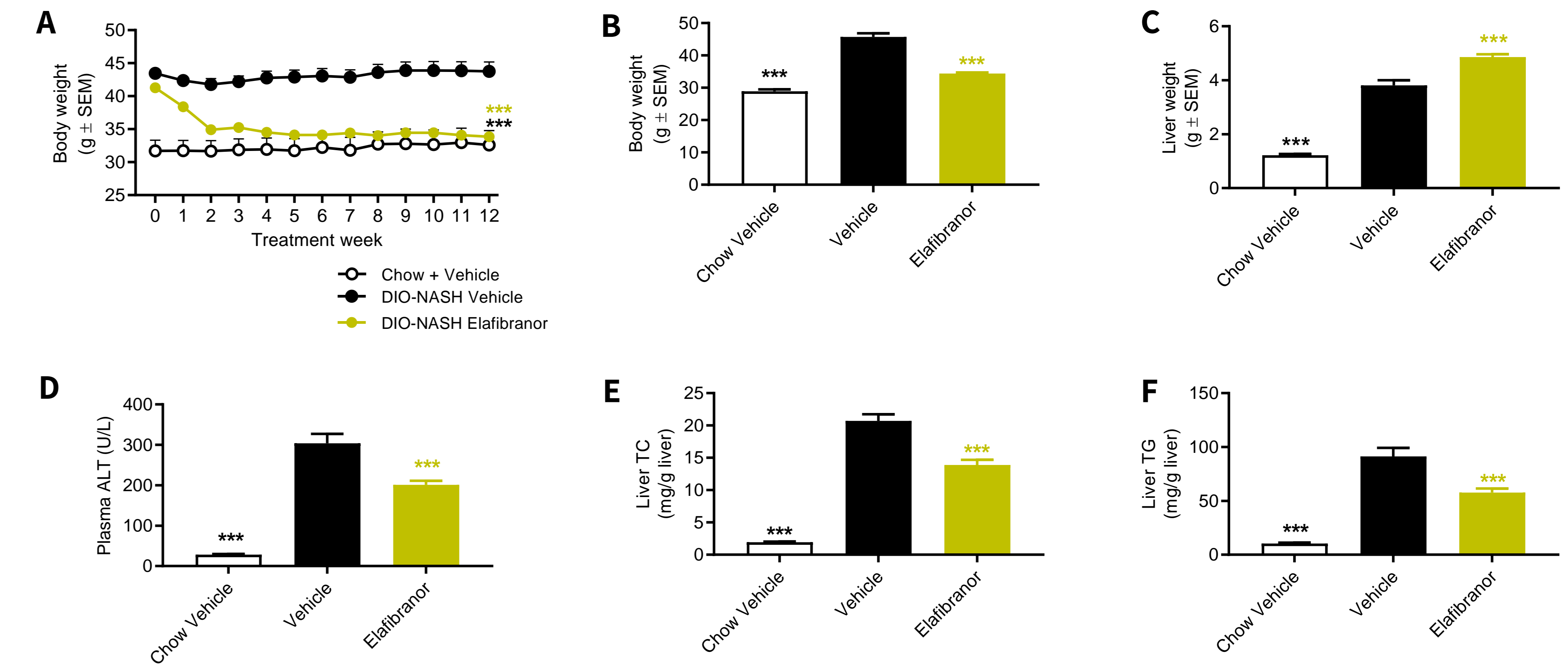
The PPAR- $\alpha/\delta$  agonist elafibranor has recently been clinically evaluated in the phase 3 study RESOLVE-IT trial in NASH patients with liver fibrosis. The present study aimed to (i) evaluate the metabolic, biochemical and histopathological effects of Elafibranor treatment in the Gubra-Amylin NASH (GAN) diet-induced obese (DIO) mouse model of fibrosing NASH; and (ii) compare to primary outcomes in the RESOLVE-IT NASH trial.

## 1 Study outline



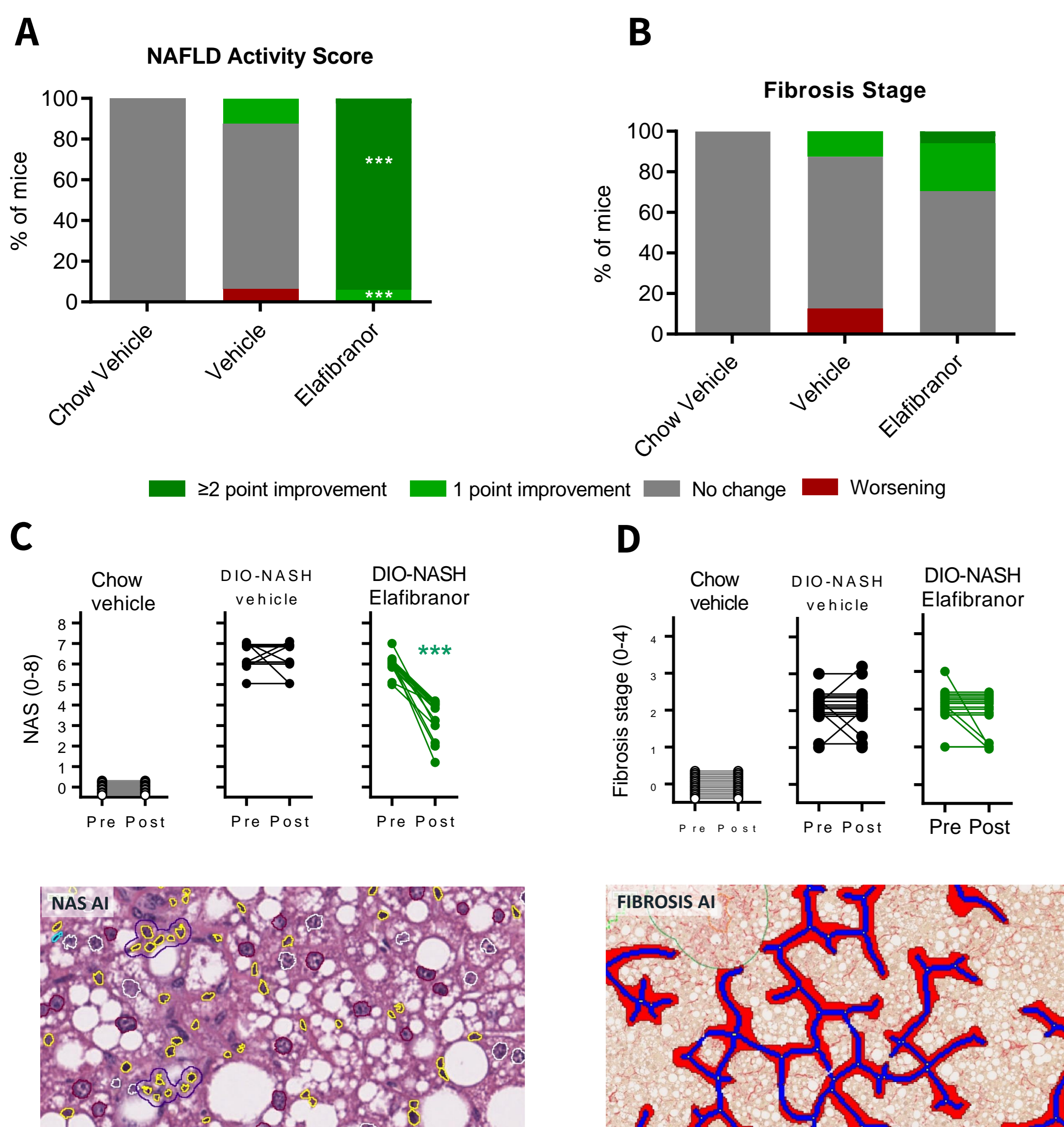
Group	Animal	Gender	Number of animals	Treatment	Administration route	Dosing Frequency	Dose
1	LEAN-CHOW	Male	10	Vehicle	PO	QD	-
2	DIO-NASH	Male	16	Vehicle	PO	QD	-
3	DIO-NASH	Male	17	Elafibranor	PO	QD	30mg/kg

## 2 Metabolic and biochemical parameters



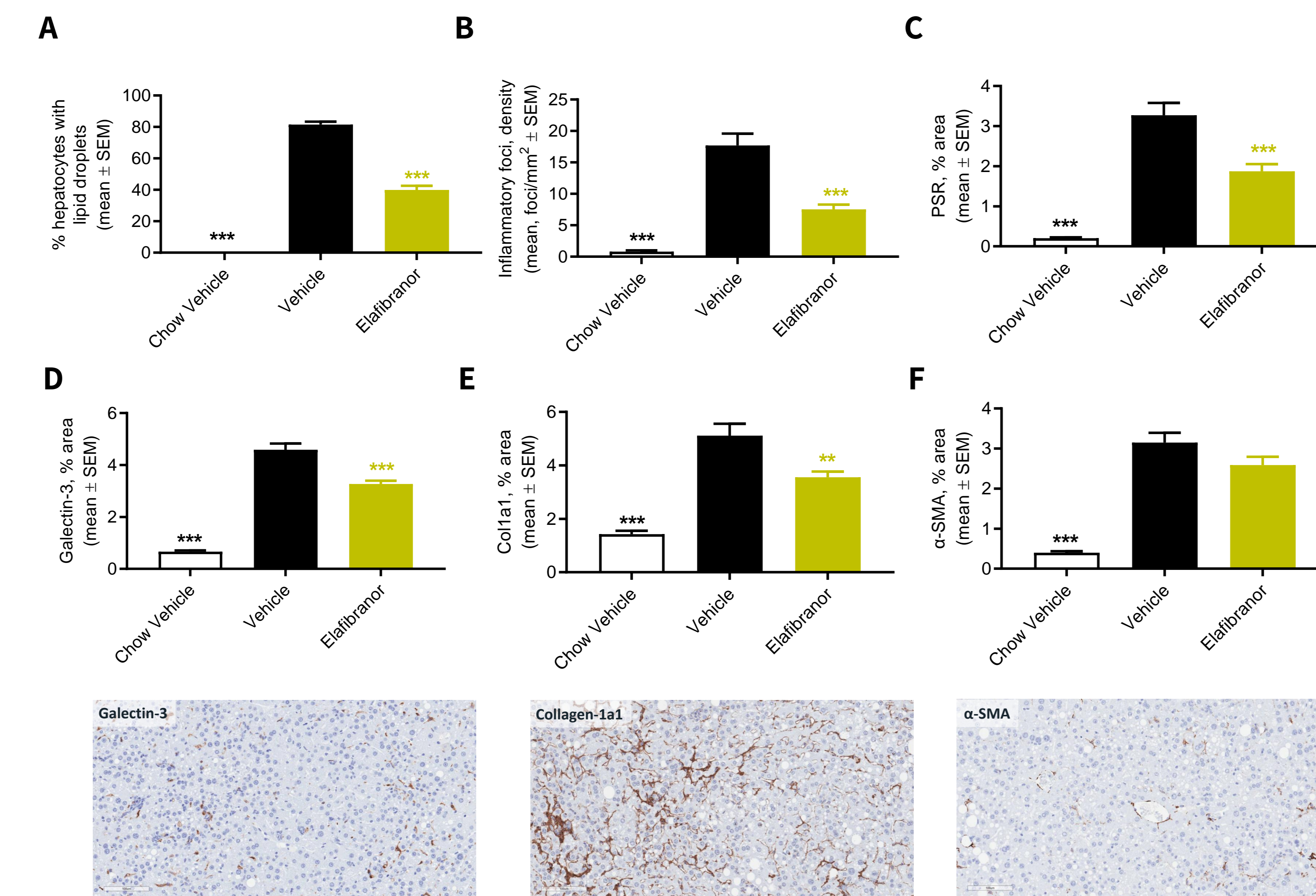
**Figure 1. Elafibranor improves metabolic and biochemical parameters in GAN DIO-NASH mice.** (A) Absolute body weight during study period. (B) Terminal body weight. (C) Terminal liver weight. (D) Terminal plasma alanine aminotransferase (ALT). (E) Terminal liver total cholesterol. (F) Terminal liver triglycerides. \*\*\*p<0.001 compared to corresponding vehicle control (Dunnett's test one-factor linear model).

## 3 NAFLD Activity Score and Fibrosis stage



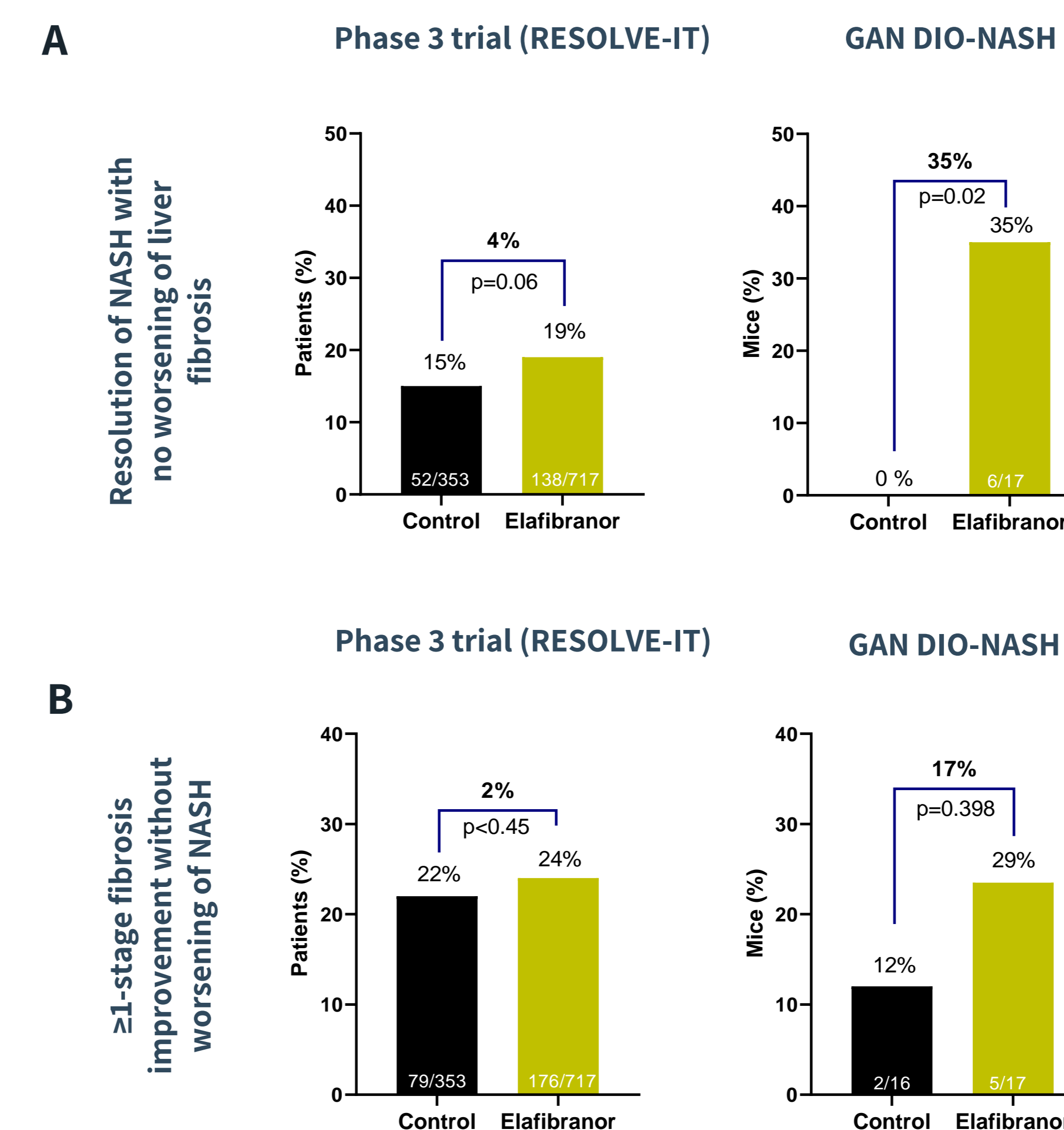
**Figure 2. Elafibranor improves NAFLD Activity Score in GAN DIO-NASH mice.** Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. (A) NAFLD Activity Score (NAS). (B) Fibrosis stage. (C, D) Comparison of individual pre-post NAS and individual pre-post Fibrosis stage. \*p<0.05, \*\*\*p<0.001 to corresponding DIO-NASH vehicle group (One-sided Fisher's exact test with Bonferroni correction). Bottom panels: representative HE and PSR photomicrographs used for GHOST evaluation.

## 4 Quantitative histological markers of steatosis, inflammation and fibrosis



**Figure 3. Elafibranor decreases histological markers for steatosis, inflammation and fibrosis in GAN DIO-NASH mice.** Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-F). (A) % hepatocytes with lipid droplets. (B) Number of inflammatory foci. (C) % area of PSR. (D) % area of galectin-3. (E) % area of collagen-1a1. (F) % area of alpha-smooth muscle actin ( $\alpha$ -SMA) as marker for stellate cell activation. Mean  $\pm$  SEM. \*p<0.05, \*\*p<0.01, \*\*\*p<0.001 to corresponding vehicle group (Dunnett's test one-factor linear model). Bottom panels: Representative galectin-3, collagen 1a1 and  $\alpha$ -SMA photomicrographs for elafibranor treatment group (scale bar, 100  $\mu$ m).

## 5 Clinical translatability



**Figure 4. Elafibranor exerts differential effects for NASH resolution and resembling effects on fibrosis improvement in GAN DIO-NASH mice versus NASH patients.** (A) Resolution of NASH (inflammation score  $\leq 1$ ; hepatocyte ballooning=0, with at least a 2-point reduction in NAS) with no worsening of liver fibrosis for elafibranor in GAN DIO-NASH mice compared to clinical phase-3 trial data (RESOLVE-IT). (B)  $\geq 1$ -stage fibrosis improvement without worsening of NASH in GAN DIO-NASH mice compared to clinical phase-3 trial data (RESOLVE-IT).

## CONCLUSION

- + Elafibranor reduces body weight, plasma ALT and liver TC and TG content.
- + Elafibranor demonstrates  $\geq 2$ -point significant improvement in NAFLD Activity Score.
- + Elafibranor did not improve Fibrosis Stage.
- + Elafibranor reduces quantitative histological markers of steatosis, inflammation and fibrosis.
- + Elafibranor improves primary outcomes for NASH resolution in GAN DIO-NASH mice, but not NASH patients.
- + Elafibranor do not improve primary outcome for fibrosis stage in both GAN DIO-NASH mice and in NASH patients.
- + Level of efficacy for elafibranor treatment on histopathological scoring in GAN DIO-NASH mice resembles fibrosis outcomes in the RESOLVE-IT phase-3 trial in NASH patients with liver fibrosis.